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| 1634 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/912,968 | DOTSON ET AL. | |
| | Examiner | Art Unit | |
| | Sarae Bausch | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *35-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Currently, claims 35-52 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but were found insufficient to place the instantly examined claims in condition for allowance. The following rejections are either newly presented or are reiterated from the previous office action. They represent the complete being presently applied to the instantly examined claims. Response to arguments follow. This action is Non-Final.

### *Withdrawn Rejections*

2. The rejections of claim 50, under 35 U.S.C. 112, first paragraph for failing to comply with the written description requirement for new matter made in section 4, page 3-4 of the previous office action, is withdrawn in view of the amendment to the claims.

3. The rejection to claims 35-37, 41-42, 45-49 under 35 U.S.C. 102(b), made in section 10, page 12-13 of the previous office action, is withdrawn in view of the arguments made at made in section B, page 17-18 of the response mailed 11/28/2005. The arguments were found persuasive as Chelley does not teach a transgenic nucleic acid and as such the rejection has been withdrawn.

### *New Grounds of Rejection*

### *Claim Rejections - 35 USC § 112 – Written Description*

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 50 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 50 is drawn to a primer pair and a corresponding labeled probes which hybridizes under stringent conditions to a nucleic acid of a 3' untranslated sequence of a 3' end of the Pisum sativum rbcS E9 gene that detects a transgenic nucleic acid molecule. The specification defines Seq ID No. 2, as the 3' untranslated region of P. sativum rbcS E9 gene (see page 27, table 1), teaches probes and primers to SEQ ID No. 2 (SEQ ID No. 7-9 and 28). However, the recitation of "hybridizes under stringent hybridization conditions" allows for polynucleotides with substantial variation with regard to 3' end of the P. sativum rbcS E9 gene. While the specification teaches examples of appropriate stringency hybridization conditions (page 13, lines 9-13), it fails to set forth a clear definition for the term "stringent conditions" and thus the metes and bounds of the conditions encompassed allow for polynucleotides with substantial variation with regard to the 3' untranslated sequence of the 3' end of the P. sativum rbcS E9 gene. The claim broadly encompasses any sequences that will hybridize to "a" nucleic acid of "a" 3' end of the P. sativum rbcS E9 gene which encompass nucleic acid sequences that are not limited to SEQ ID NO: 2, 7-9 and 28. Thus, the claim broadly encompasses sequences of any magnitude and/or content that can hybridize to the 3' end of the P. sativum rbcS E9 gene and detect a transgenic nucleic acid molecule. Even stringent hybridization would tolerate mismatches and result in sequences that correspond to mutants, variants, and homologs of the 3' end of the *Pisum sativum*

rbcS E9 gene, which is not disclosed in the specification. The claim language encompasses sequences that correspond to mutated fragments, allelic variants, splice variants, genomic sequence, sequences from other species and so forth that would not detect a transgenic nucleic acid molecule and thus the claim encompasses sequences not described by the specification. Further, the additional sequences that are encompassed by the broad genus of the claim reads on sequences that can hybridize to different sequences, different regions of the gene which have a different function than to hybridize to the 3' end of the P. sativum rbcS E9 gene and detect a transgenic nucleic acid molecule. The specification provides insufficient written description to support the genus encompassed by the claim.

The instant claim is drawn to undisclosed sequences encoding modification that have not been contemplated. The specification provides insufficient written description to support the genus encompassed by the claim. Absent a written description, the specification fails to show that the applicant was "in possession of the claimed invention" at the time the application for the patent was filed. Further, the genus of polynucleotides comprised by the claim is a large variable genus, which can potentially encode proteins of diverse functions and read on genomic sequences. The specification only discloses a selected number of species of the genus; i.e. SEQ ID NO 2 (SEQ ID 7-9 and 28, which are part of SEQ ID NO 2), which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the genus. Thus one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed with respect to claim 50.

*Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was

in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116.)

With the exception of SEQ ID NOS: 2, 7-9, and 28 the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993), and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. In *Fiddes v. Baird*, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1404, 1405 held that:

> To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Accordingly, the specification does not provide a written description of the invention of claim 50.

***Response to Arguments***

6. The response traverses the rejection on pages 9-13 of the response mailed 11/28/2005. The response asserts on page 9 that the P. satvium rbcS E9 nucleotide sequence has been described previously and that the specification provides disclosure such that a person of ordinary skill in the art would understand that Applicants had possession of the claimed invention. The response further asserts on page 10 that the specification describes gene sequences, of the P. sativum rbcS E9 gene, appropriate hybridization conditions, and oligonucleotides that hybridize to the 3' untranslated regions. This response has been thoroughly reviewed but not found persuasive. It is noted that the P. sativum rbcS E9 gene was known and the 3' untranslated region of the rbcS E9 gene was described in the prior art, however the specification does not describe a representative number of primers and probes that hybridize to the 3' untranslated region of the rbcS E9 gene and detect a transgenic nucleic acid molecule. The specification teaches only SEQ ID No. 2 and SEQ ID No. 7-8 and 28, which are identical to regions within SEQ ID No. 2 and the terminology "hybridization" allows for mismatches within SEQ ID No. 2, which encompasses sequences that are not identical SEQ ID No. 2, sequences from other species, mutated fragment sequence, allelic variants, genomic sequences that are not described in the specification.

The response asserts on page 11, that Applicant is not required to describe each and every one of the molecules claimed. The response further asserts on page 12 that Applicant discloses a structural feature, SEQ ID No. 2 and this feature provides a basis for each and every nucleic acid molecule in the claimed genus. This response has been thoroughly reviewed but not found

persuasive. It noted that Applicant is required to describe a representative number of species in the claimed genus and the specification does not describe a representative number of sequences that would hybridize under stringent conditions to the 3' untranslated region of the 3' region of the rbcS E9 gene that would detect a transgenic nucleic acid molecule. One of ordinary skill in the art would not know which sequences would be encompassed by the genus as the claim is drawn to nucleic acid molecules that hybridize under stringent conditions and the specification does not define stringent conditions, the specification merely gives an example of stringent conditions.

The response asserts on page 12, that the specification can not fail to meet the written description requirement simply because it does not reiterate the structure or formula or chemical name for known nucleotide sequences. It is noted that the rejection was not made because the specification does not reiterate the structure of chemical name for known nucleotide sequences, the specification lacks written description because it does not describe a representative number of sequences that would hybridize under stringent conditions to the 3' untranslated region of the 3' end of the P. sativum rbcS E9 gene and detect a transgenic nucleic acid molecule. The specification fails to set forth a clear definition for the term "stringent conditions" and thus the metes and bounds of the conditions encompassed for hybridization allow for polynucleotides with substantial variation with regard to the 3' untranslated sequence of the 3' end of the P. sativum rbcS E9 gene. Even stringent hybridization would tolerate mismatches and result in sequences that correspond to mutants, variants, and homologs of the 3' end of the *Pisum sativum* rbcS E9 gene, which is not disclosed in the specification. Further, the additional sequences that are encompassed by the broad genus of the claim reads on sequences that can hybridize to

different sequences, different regions of the gene which have a different function than to hybridize to the 3' end of the P. sativum rbcS E9 gene and detect a transgenic nucleic acid molecule. The specification provides insufficient written description to support the genus encompassed by the claim.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

***New Grounds of Rejections***

***Claim Rejections - 35 USC § 102***

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim 50 is rejected under 35 U.S.C. 102(b) as being anticipated by 1997 Biochemicals Catalog of Boehringer Mannheim.

Boehringer Mannheim teach a hexanucleotide mixture of all possible sequences for random-primed DNA labeling. The hexanucleotide mixture is a kit that would detect a transgenic nucleic acid molecule that would hybridize to the 3' untranslated sequence of a 3' end of the P. sativum rbcS E9 gene and comprises one primer pair and labeled probe since it contains all possible sequences of hexamers, which would encompass at least one primer pair and labeled probe (a hexamer that is partially complementary to the sequence of the 3' untranslated sequence of a 3' end of the P. sativum rbcS E9 gene with the mismatch nucleotide being the label). See page 95, Hexanucleotide Mix, Boehringer Mannheim 1997 Biochemical Catalog.

## *Maintained Rejections*

### *Claim Rejections - 35 USC § 102*

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 35-37, 41-42, 45-46 and 48-50 are rejected under 35 U.S.C. 102(b) as being anticipated by Fleming et al. (The Plant Journal (1996) 10(4), pp. 745-754).

With regard to claim 35-36, 41, and 45-46, Fleming et al. teach a method of RT-PCR analysis of gene expression of rbcS genes in transgenic plants (see summary and 2nd column, 1st paragraph, page 745). Fleming et al. teach reverse transcription of each rbcS gene (first transgenic nucleic acid) followed by PCR (instant claim 41-42) of the cDNA from each RNA sample using a common 5' primer for the coding region and a gene-specific 3' primer for each of the 3' UTR of the genes of rbcS (see page 752, RT-PCR cont'd to page 753 and figure 5). Fleming et al. teach following amplification the PCR reaction products were blotted on a nylon membrane, hybridized with a labeled DNA body probe for rbcS that bound all amplified rbcS sequences (second transgenic nucleic acid, signal sequence) (instant claim 36 and 49) and estimating signal intensity for each sample (see page 753, 1st column, 1st full paragraph) (quantitation of mRNA transcribed from second transgenic nucleic acid molecule)(instant claim 37, 45-46).

Alternatively, Fleming et al. teach a method of semi-quantitative RT-PCR analysis of gene-specific rbcS transcript levels (see page 748, 2nd column, 1st full paragraph) (claim 42). Fleming et al. teach RT-PCR (claim 41) analysis of ribosomal protein mRNA, rpl2 (rpl2 mRNA is the second transgenic nucleic acid, signal sequence) (claim 36-37) and analyzing rbcS gene-specific transcript levels (rbcS transcripts are the first transgenic nucleic acid) (see figure 4a-e). Fleming et al. teach that the rbcS genes are expressed relative to the signal obtained using the rpl2 primers at the same dilutions (see page 749, 1st column, 2nd paragraph). Fleming et al. teach that rbcS gene-specific transcript levels are expressed relative to the signal obtained using the RPL2 primers at corresponding sample dilutions (detecting expression of second transgenic nucleic acid which indicates expression of first transgenic nucleic acid) (see page 749, 1st column, 2nd paragraph and figure 4).

With regard to claim 47, Fleming et al. teach a pair of oligonucleotide primers and an oligonucleotide probe designed to hybridized to the second transgenic nucleic acid molecule, with regard to the recitation of "designed to hybridize to said second transgenic nucleic acid molecule in a 5' nuclease assay" in claim 47 line 2, is not given patentable weight due to an intended use that does not occur in the method (figure 4-5 and see page 752, RT-PCR cont'd to page 753).

***Response to Arguments***

11. The response traverses the rejection on page 13-17 of the response mailed 11/28/2005. The response asserts on page 14 that there is no indication in the reference that the plants that were analyzed by RT-PCR were transgenic. The response asserts that the authors "developed an RT-PCR analysis which would provide with data on the time-dependent accumulation of specific

RBCS transcripts during leaf primordium development". The response asserts that Fleming does not indicate that RT-PCR was performed on nucleic acids obtained from transgenic plants. The response asserts that the disclosure of Fleming et al. suggests that the nucleic acids for use in RT-PCR were obtained from transformed plants. This response has been thoroughly reviewed but not found persuasive. Fleming et al. does that that the nucleic acids for use in RT-PCR were transgenic nucleic acids, as defined by the specification. Fleming et al. state "in order to analyze the regulatory elements involved in generation of this pattern, we decided to examiner reporter gene (GUS) expression in transgenic plants under the control of RBCS promoter sequence" (see 2nd column, page 745). Furthermore, Fleming teaches that the transgenic plants containing the tomato RBCS 5' sequences were constructed as described by Meier et al. (see plant material and tissue culture, page 752). Additionally, Fleming et al. teach RT-PCR of RBCS gene expression in tomato, which was described in the experimental procedures as a transgenic plant containing the tomato RBCS 5' sequence (see page 751, RBCS gene expression in developmentally controlled leaf initiation). Therefore, Fleming et al. teaches RT-PCR methods that detect expression of a first transgenic nucleic acid molecule as defined by the specification.

The response asserts on page 15, last paragraph, that Fleming et al. does not teach hybridization of second transgenic to indicate the expression of a first transgenic nucleic acid molecule. The response asserts that the resulting amplification product includes sequences from the coding sequence of the rbcS or 1st transgenic nucleic acid molecule and therefore is not designed to hybridize to the second transgenic nucleic acid molecule. This response has been thoroughly reviewed but not found persuasive as claims only require amplification of the cDNA and hybridization of said cDNA with at least one oligonucleotide designed to hybridize to the

second transgenic nucleic acid whereby hybridization indicates expression of the 1st transgenic nucleic acid sample and Fleming teaches amplification of the cDNA (rbcS 3' UTR regions of each gene) and hybridization of the cDNA with at least one oligonucleotide designed to hybridize to the second transgenic nucleic acid (DNA body probe) to indicate expression of the 1st transgenic nucleic acid sequence (each rbcS genes) (see page 753, 1st full column, 1st paragraph).

The response asserts on page 16, 2nd full paragraph that the RPL2 or rbcS sequence is not transgenic as the response asserts that the RPL2 amplification product is used as an internal control to determine the relative level of expression of the native rbcS gene. This response has been thoroughly reviewed but not found persuasive. As defined in the specification, page 6 the second transgenic nucleic acid molecule means any transgenic nucleic acid molecule that is conveniently used as a surrogate indicator for a first transgenic nucleic acid molecule and may be one of the more commonly used DNA elements used in recombinant DNA methods, including promoters, regulatory elements, markers, and may be the same species as the host, enable incorporation of the first transgenic nucleic acid molecule into the host genome (see page 6, last paragraph cont'd to page 7). Therefore, the RPL2 amplification product, which is located within the transgenic plant is a second transgenic nucleic acid, as defined by the specification.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

12. The rejections of claims 35, 41, 47, and 49 under 35 U.S.C. 102(b) as being anticipated over Hamilton et al (*Gene*, 1997) in the previous office action, is maintained and incorporated herein (see page 8-9 of previous office action mailed 3/22/2004).

Hamilton demonstrates the expression of transgenes in a BIBAC vector (p. 113, 2nd column, 3rd paragraph), wherein a successful transfection into the host plant is determined based upon the following transgenic nucleic acids: *sacB* gene, GUS-NPTII gene (beta-glucuronidase – neomycin phosphotransferase II), and the HYP gene (hygromycin phosphotransferase). In one example, the first transgenic nucleic acid is the *sacB* gene and the second transgenic acid is the GUS-NPTII and/or HYG gene:

> Potential transgenic plants were initially tested by PCR using primers to the GUS-NPTII and HYG [...]. [...] Plants that tested positive for the BIBAC T-DNA by PCR [*thereby amplification, claim 35 step ii, and claim 41*] were all verified by Southern analysis [*thereby hybridization, claim 35 step iii, and claim 49*] using a NPTII specific probe. (p. 113, 1st column, 3rd paragraph)(see also figure 3).

As such, the method includes a primer pair and probe (*claim 47*). (Note: The claim language "designed to hybridize to a nucleic acid molecule in a 5' nuclease assay" in claim 47 line 2, is not given patentable weight due to an intended use that does not occur in the method claimed. In addition, the oligonucleotide need only be "designed" to hybridize to the mRNA, this does not indicate that it is within the sample and hybridizing to the mRNA, merely it is capable of doing so if in the same sample.) A second example of the method demonstrated is wherein the first transgenic nucleic acid corresponds to large DNA inserts into the BIBAC1 and BIBAC2 plasmids. The second transgenic nucleic acid corresponds to the GUS-NPTII. Hamilton

demonstrates in "[f]igure 4b and c shows the hybridization of BIBAC DNA to a GUS-NPTII-specific probe and a HYG-specific probe, respectively" (p. 113, 2nd column, 2nd paragraph).

***Response to Arguments***

The response asserts on page 19, 2nd-3rd paragraph, that Hamilton et al. does not include all the limitations of the present claims. The response asserts that the examiner has not pointed to any support that Hamilton discloses a method comprising providing a complementary DNA. The response asserts on page 19, last paragraph continued to page 20, that the skilled artisan would recognize that Southern analysis does not indicate expression of the hybridized nucleic acid molecule and Hamilton discusses the Southern analysis was performed to verify that the BIBAC vector were integrated into the plant genome during transformation and as such Hamilton does not teach a method to detect expression of a transgenic nucleic acid molecule. This response has been thoroughly reviewed but not found persuasive as one of skill in the art would recognize that the southern analysis step of Hamilton inherently teaches hybridization of the nucleic acid molecule which would indicate expression of the nucleic acid molecule. As stated in the previous office action, claim 35 does not require that the step of "providing a complementary DNA of the mRNA" be limited to the reverse transcription step of RT-PCR due to the dependency of claim 41. Claim 41 states the "amplifying" step, step ii of claim 35, be either PCR or RT-PCR. Accordingly, claim 35 has been broadly interpreted to encompass any means of "providing a complementary DNA of the mRNA" which includes providing genomic DNA as DNA is "inherently complementary" to mRNA. The southern analysis step of Hamilton inherently teaches hybridizing said complementary DNA with at least one probe designed to hybridize to said second transgenic nucleic acid.

As stated in the previous office action, Hamilton teaches that plants that tested positive for BIBAC T-DNA by PCR were verified by southern analysis using a NPTII probe and southern analysis is a technique that detects expression of a sequence by hybridization of the probe, NPTII, to the target nucleic acid sequence. If the nucleic acid was not expressed southern analysis would not have detected the sequence. Hamilton teaches in figure 4 of the nucleic acids that were expressed in the transgenic plant were analyzed and detected by southern analysis. Furthermore, Hamilton demonstrates the expression of transgenes in a BIBAC vector (p. 113, 1st column, 3rd paragraph), wherein a successful transfection into the host plant is determined based upon the following transgenic nucleic acids: *sacB* gene, GUS-NPTII gene (beta-glucuronidase – neomycin phosphotransferase II), and the HYP gene (hygromycin phosphotransferase). In one example, the first transgenic nucleic acid is the *sacB* gene and the second transgenic acid is the GUS-NPTII and/or HYG gene:

> Potential transgenic plants were initially tested by PCR using primers to the GUS-NPTII and HYG [...]. [...] Plants that tested positive for the BIBAC T-DNA by PCR [*thereby amplification, claim 35 step ii, and claim 41*] were all verified by Southern analysis [*thereby hybridization, claim 35 step iii, and claim 49*] using a NPTII specific probe. (p. 113, 1st column, 3rd paragraph)(see also figure 3).

A second example of the method demonstrated is wherein the first transgenic nucleic acid corresponds to large DNA inserts into the BIBAC1 and BIBAC2 plasmids. The second transgenic nucleic acid corresponds to the GUS-NPTII. Hamilton demonstrates in "[f]igure 4b and c shows the hybridization of BIBAC DNA to a GUS-NPTII-specific probe and a HYG-specific probe, respectively" (p. 113, 2nd column, 2nd paragraph). At page 113, 1st column, Hamilton et al. teaches amplifying the second transgenic nucleic acid (primers to Gus-NPTII)

and using a probe to NPTII (again to second transgenic nucleic acid). Hamilton et al. anticipates claims 35, 41, 47, and 49 and the rejection is maintained.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

***Claim Rejections - 35 USC § 103***

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 35-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hunt et al (*DNA*, 1988) in view of Freeman et al. (*Biotechniques*, 1999).

Hunt et al demonstrates the transformation of a tobacco plant with a plasmid carrying the 3'noncoding strand of the pea rbcS-E9 3'region (*claims 37, 38*) which aligns 99.5% with SEQ ID NO: 2 (a 637 bp sequence) from residue 1-633 (*claim 39*), and a desired transgene pAH10 (figure 2A). Due to claim 39 reciting the phrase "has a sequence" (line 2), the claim comprises fragments and sequences greater and smaller than the elected sequence. For example, the recitation of "has a sequence of SEQ ID No. 2" encompasses even two nucleotides of SEQ ID NO: 2. (An amendment to the claim language to recite, "has **the** sequence selected from" is suggested). The reference further teaches the oligonucleotides of claims 40, 44, 51, and 52 wherein SEQ ID NO: 7, 9, 8 (which align at residues 27-49, 51-76, and 77- 102 respectively) are

encompassed by the sequence displayed in figure 2. The rbcS region is representative of the 2nd transgenic nucleic acid as per claim 35 and the pAH10 is the 1st transgenic nucleic acid. In addition, the indicated region has greater than 15 and greater than 100 contiguous base pairs that are substantially identical to SEQ ID NO: 2 (*claims 43, 44*). Hunt detects the rbcS by the S1 nuclease assay (p. 331, 1st –2nd column, *RNA isolations and S1 nuclease protection analysis*) where in Klenow was utilized (therefore amplification) for radiolabeling the oligonucleotides with radiolabels such as [alpha-32P]dATP or dCTP as required by claims 45 and 46; and probes were hybridized (claim 35) to the rbcS region for protection during the S1 nuclease thereby detecting the 2nd transgenic nucleic acid and the 1st transgenic nucleic acid.

Hunt does not teach the amplification by PCR or RT-PCR, quantitative and competitive RT-PCR, or the primers utilized for the amplification.

Freeman teaches the benefits of PCR, specifically utilizing quantitative RT-PCR, both competitive and non-competitive (pp. 116-117) to quantify mRNA (*claims 36, 41, 42*).

> Reverse transcription PCR (RT_PCR) represents a sensitive and powerful tool for analyzing RNA. [abstract]. No other techniques offers the potential to rapidly and quantitatively analyze a number of gene products from multiple small samples in a multiplex format. (p. 122, 3rd column, last paragraph).

On page 113, Freeman teaches designing primers for the use in such an assay to be gene specific or non-specific however if specific then it "increases specificity and decreases background associated with other types of primers" (3rd column, 1st – 2nd paragraph). Means of detecting the amplified products are taught to be hybridization based assays such as Southern Blots or fluorescence detection (p. 114, 2nd column, 1st paragraph). Sequence specific probe design for

detection of the amplified products is taught on page 114 (2nd column, 2nd paragraph), wherein the probe has a detectable fluorophoric label.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention was made to improve the detection method of Hunt et al and further modify the mRNA expression analysis to utilize quantitative RT-PCR which includes amplification along with primers and probes designed for quantitative RT-PCR as per the teachings of Freeman et al. because Freeman teaches that quantitative RT-PCR provides increased sensitivity in mRNA detection. With regard to claim 39 and the sequence of the second transgenic nucleic acid, the claim comprises fragments and sequences greater and smaller than the elected sequence comprising such fragments thus it encompasses even a two nucleotide sequence of SEQ ID NO: 2 since a fragment remains inclusive of a sequence of shorter length with each base pair matched with the base pairs of the elected sequence. With regard to the oligonucleotides (primers/ probes) of claim 40, it would have been further *prima facia* obvious to one of ordinary skill in the art to design primers and probes for use in the method of Hunt in view of Freeman. The ordinary artisan would be motivated to generate probes and primers for the improved method of RNA detection of Hunt in view of Freeman, and in doing so, would generate a number of probes and primers including those with SEQ ID NO: 7, 8, 9 and 28 for use in the RNA detection method of Hunt and Freeman. These sequences are considered functionally equivalent in carrying out the amplification and detection step in the RT-PCR method for detection the 3'noncoding strand of the pea rbcS-E9 3'region of Hunt in view of Freeman, absent secondary considerations. An ordinary artisan would have been motivated to use quantitative RT-PCR amplification process instead of the S1 nuclease assay in the detection method of Hunt et al, for

increased specificity and decreased background as per the teachings of Freeman et al. [As shown above, the primers and probes, SEQ ID NO: 7, 9, 8, align at residues 27-49, 51-76, and 77- 102 respectively]. One of ordinary skill in the art would have been motivated to do RT-PCR RNA analysis taught by Freeman et al due to the advantages of improved RNA analysis and detection because:

> Reverse transcription PCR (RT_PCR) represents a sensitive and powerful tool for analyzing RNA. [abstract]. No other techniques offers the potential to rapidly and quantitatively analyze a number of gene products from multiple small samples in a multiplex format. (p. 122, 3rd column, last paragraph).

***Response to Arguments***

The response asserts on page 21, last paragraph, that the cited references do not teach or suggest the claimed invention. The response asserts on page 22 continued to page 23 that Hunt does not disclose or suggest a method for detecting expression of a first transgenic nucleic acid molecule and assert that the examiner has not cited any support for the proposition that the methods discussed in Hunt were not sufficient to solve the problem faced in Hunt and would therefore require improvement. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is noted that the rejection does not suggest that the method of Hunt needs to be improved or that one Hunt is insufficient, the rejection merely states that one of skill in the art would have been motivated to improve the method of Hunt to include a method that allows for increased sensitivity of mRNA detection and one of skill in the art would have been motivated to combine

the teaching of Hunt with Freeman. Furthermore, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to improve the detection method of Hunt and further modify the mRNA expression analysis to utilize quantitative RT-PCR which includes amplification along with primers and probes designed for quantitative RT-PCR as per the teachings of Freeman et al. because Freeman teaches that quantitative RT-PCR provides increased sensitivity in mRNA detection.

The response asserts that the Examiner's conclusion of obviousness is based on improper reasoning and misinterpretation of the art. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971

The response asserts on page 23, 1st full paragraph, that the modifications of Hunt proposed by the Examiner would render the reference unsatisfactory for its intended purpose. The response asserts that S1 nuclease assay was performed to identify 3' ends in the rbcS 3' region and that modifying Hunt as suggested to use RT-PCR would not identify the 3' ends. As stated in MPEP 2145 [R-2], Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See MPEP § 2129 and § 2144.03 for a discussion of admissions as prior art. The arguments of counsel cannot take the

place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness."). See MPEP § 716.01(c) for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration. In the instant case, the attorney's argument is not factual evidence and requires an appropriate affidavit or declaration to be of probative value which includes unexpected results and inoperability of the prior art. This should not be construed as an invitation for providing evidence. As further stated in the MPEP 716.01 regarding the timely submission of evidence:

A) Timeliness.
Evidence traversing rejections must be timely or seasonably filed to be entered and entitled to consideration. In re Rothermel, 276 F.2d 393, 125 USPQ 328 (CCPA 1960). Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted:
(1) prior to a final rejection,
(2) before appeal in an application not having a final rejection, or
(3) after final rejection and submitted
(i) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection, or
(ii) with a satisfactory showing under 37 CFR 1.116(b) or 37 CFR 1.195, or
(iii) under 37 CFR 1.129(a).

Further, the method of Hunt identifies and detects the 3' region of the rbcS-E9 gene by using a nuclease assay and modifying Hunt to use a more efficient method of RT-PCR instead of a nuclease assay would result in the same identification of the 3' region of the rbcS-E9 gene. Furthermore, Hunt et al. disclose a method for detecting the expression of a first transgenic nucleic acid molecule in a sample by hybridizing a complementary DNA of mRNA transcribed

from a second transgenic nucleic acid molecule with at least one oligonucleotide designed to hybridize to the second transgenic nucleic acid molecule (see section 13, 1st paragraph Response to Arguments, instant office action).

The response asserts on page 23, last paragraph that the response asserts on page 12, 1st paragraph, that even if the combination is proper, the combination does not render the claim obvious. The response asserts that Hunt et al. and Freeman et al. do not teach or suggest a method a method to detect the expression of the first transgenic nucleic acid molecule in a sample by hybridizing a complementary DNA of mRNA transcribed from a second transgenic nucleic acid molecule with at least one oligonucleotide designed to hybridize to the second transgenic nucleic acid molecule wherein hybridization indicated expression of the first transgenic nucleic acid molecule. This traversal has been thoroughly viewed but was not found persuasive. As stated in the previous office action, Hunt does teach a method of identifying the 3' end of pea rbcS-E9. Hunt does teach that the 3' region of the pea rbcS-E9 gene does contain a number of discrete, cryptic polyadenylation sites, but in order to determine that the 3' end of the pea rbcS-E9 gene does contain these sites, the 3' end of pea rbcS-E9 must be identified and detected and therefore Hunt et al. teach a method of detecting the expression of a first transgenic nucleic acid molecule by detecting the 3' end of the rbcS-E9 gene.

The response asserts on page 24, last paragraph, that the skilled artisan would not turn to Hunt et al. to solve the problem of detecting the expression of a first transgenic nucleic acid molecule. The response further asserts that Hunt et al. is a different field of endeavor from the claimed invention. This response has been thoroughly reviewed but not found persuasive. As stated in the previous office action, it has been held that a prior art reference must either be in

the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Hunt et al. is analogous art as it employs nucleic acid detection of transgenic plant gene expression, which is the same field as applicant's endeavor. Further, Hunt et al. disclose a method for detecting the expression of a first transgenic nucleic acid molecule in a sample by hybridizing a complementary DNA of mRNA transcribed from a second transgenic nucleic acid molecule with at least one oligonucleotide designed to hybridize to the second transgenic nucleic acid molecule (see section above, instant office action). Further, Hunt disclose detecting the gene rbcS-E9 gene which is the second transgenic nucleic acid molecule of the instant claims and therefore Hunt et al. is analogous art. With regard to the argument that Hunt is not pertinent to the particular problem that the present inventors faced, it is noted that the claims are broadly drawn to detecting any first transgenic nucleic acid by detecting any second transgenic nucleic acid. The fact that Hunt et al. in view of Freeman et al. disclose detection of specific nucleic acids does not exclude the reference as art. The claims do not specifically set forth any particular embodiments to distinguish from the teaching of Hunt and Freeman et al.

The response asserts on page 25, Freeman et al. does not make up what Hunt lacks. The response asserts that Freeman describe non-specific primers. The response asserts that the cited reference does not disclose a method for detecting expression of a first transgenic nucleic acid molecule in a sample by hybridizing a complementary DNA of mRNA transcribed from a second transgenic nucleic acid molecule with at least one oligonucleotide designed to hybridize to the second transgenic nucleic acid molecule where the hybridization indicates expression of the first

transgenic nucleic acid molecule in the sample. This response has been thoroughly reviewed but not found persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As stated in the previous office action, the reference of Freeman et al. teaches the benefits of RT-PCR to quantify mRNA. Hunt in view of Freeman et al. meets the limitations of the method for detecting the expression of a first transgenic nucleic acid molecule and Hunt in view of Freeman et al. teaches the use of RT-PCR to meet the limitations of claims 36, 41, 42, 47, 48, and 50. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to improve the detection method of Hunt and further modify the mRNA expression analysis to utilize quantitative RT-PCR which includes amplification along with primers and probes designed for quantitative RT-PCR as per the teachings of Freeman et al. because Freeman teaches that quantitative RT-PCR provides increased sensitivity in mRNA detection.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

***Conclusion***

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (571) 272-0745. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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